UNIVERSITY OF MINNESOTA
SEP
11
LIBRARY

VOLUME XIV February 1958 NUMBER 2

Clinical Proceedings

OF THE CHILDREN'S HOSPITAL

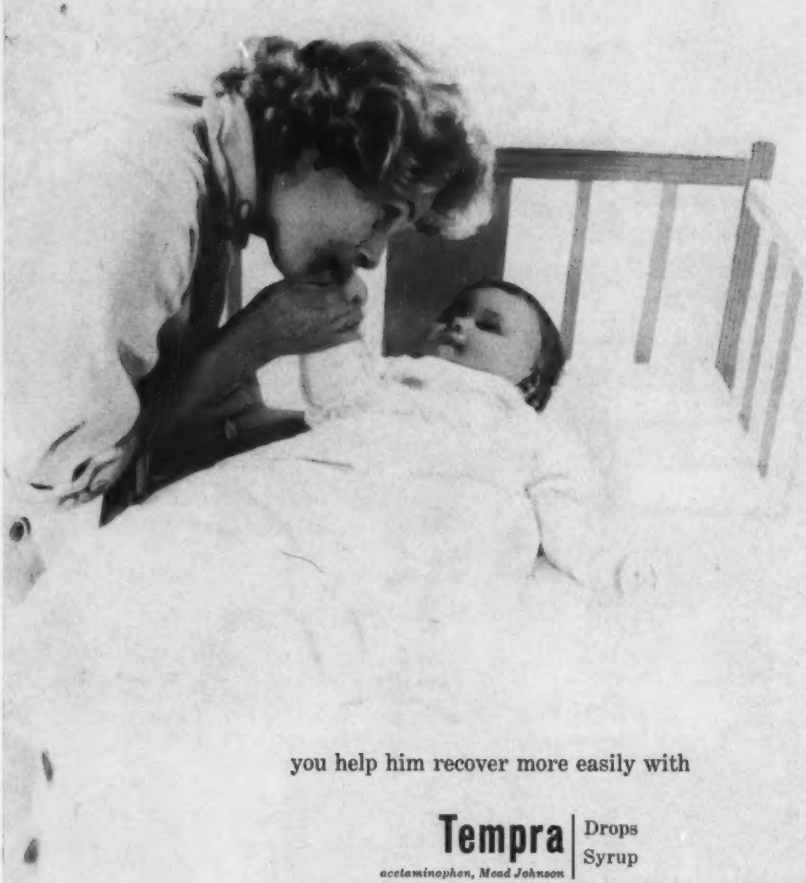
WASHINGTON, D. C.

THE RENAL OSTEODYSTROPHIES. *James A. Davis, Jr., M.D.*..... 21

HEMANGIOMAS IN CHILDHOOD. *Frederic Gerard Burke, M.D., Robert E. Moran, M.D., Naomi M. Kanof, M.D.*..... 38

CONGENITAL COMPLETE HEART BLOCK. *Uberne Valerio, M.D.*... 46

easier antipyretic/analgesic relief



you help him recover more easily with

Tempra | Drops / Syrup

acetaminophen, Mead Johnson

First physician-controlled antipyretic/analgesic in two liquid dosage forms . . . on Rx only

Wild-cherry-flavored Tempra Drops and mint-flavored Tempra Syrup are readily accepted, well tolerated. Mother appreciates that with Tempra there's no fussing, no forcing. And you have better control of medication and dosage.

Ask your Mead Johnson Representative for the new Tempra Brochure, or write to us, Evansville 21, Indiana.

MEAD JOHNSON

SYMBOL OF SERVICE IN MEDICINE

TE582

Mead Johnson & Company, Suite 422 Eig Building, 8641 Colesville Road Silver Spring, Maryland. JUniper 9-1222

CLINICAL PROCEEDINGS
OF THE CHILDREN'S HOSPITAL

2125 13th Street, N. W. Washington 9, D. C.

EDITOR FOR FEBRUARY

MILTON S. GLATT, M.D.

EDITOR-IN CHIEF

ROBERT H. PARROTT, M.D.

EDITORIAL BOARD

FREDERIC G. BURKE, M.D.
JOSEPH M. LOPRESTI, M.D.
E. CLARENCE RICE, M.D.
SYDNEY ROSS, M.D.

MANAGING EDITORS

J. WILLIAM OBERMAN, M.D.
GEORGE J. COHEN, M.D.

ASSOCIATE EDITORS

JOHN BAYLY, M.D.
STANLEY L. BLUMENTHAL, M.D.
WINSTON E. COCHRAN, M.D.
GORDON W. DAISLEY, JR., M.D.
MAX FISCHER, M.D.
MILTON S. GLATT, M.D.
GRACE H. GUIN, M.D.
JOHN O. NESTOR, M.D.
MARSHALL M. PARKS, M.D.
GEORGE WILLIAM WARE, M.D.
CHARLES R. WEBB, M.D.
RALPH D. WHITLEY, M.D.

GENERAL MANAGER

THELMA WALLER

THE RESIDENT STAFF: AUGUSTO ALVARADO, M.D., SALVATORE BATTIATA, M.D., CATHERINE P. CHESTER, M.D., VICTOR S. CIPOLLA, M.D., MITHAT CORUH, M.D., ENRICO DAVOLI, M.D., DONALD W. DELANEY, M.D., GLORIA D. ENG, M.D., JOSEPH CHARLES EVERS, M.D., SEYMOUR Z. GOLDBLATT, M.D., STANLEY GOULD, M.D., JAMES L. HATLEBERG, M.D., HYUN-WHA KIM (Oh), M.D., SHEELAGH MARSH, M.D., WILLIAM R. O'REILLY, M.D., JOHN PAPATHANASIOU, M.D., FRANCISCO PEREZ-TURLAY, M.D., DONALD R. POHL, M.D., BYRON D. ROSEMAN, M.D., J. WILLIAM STOHLMAN, M.D., BELINDA C. STRAIGHT, M.D., LETICIA U. TINA, M.D., JOHN TKACZ, M.D., GHOLAM H. VAZINE, M.D., PIO G. VERA CRUZ, M.D., SIDNEY L. WERKMAN, M.D., LUCAS YAMMAMOTO, M.D., AND LILLIAN KOCH ZIEGLER, M.D.

PUBLICATIONS COMMITTEE OF THE MEDICAL STAFF: FREDERIC G. BURKE, M.D., PRESTON A. MCLENDON, M.D., E. CLARENCE RICE, M.D., SYDNEY ROSS, M.D., J. WILLIAM OBERMAN, M.D., AND GEORGE WILLIAM WARE, M.D.

PUBLISHED MONTHLY BY THE STAFF AND RESEARCH FOUNDATION OF THE CHILDREN'S HOSPITAL, WASHINGTON, D. C.

Cases are selected from the weekly conferences held each Friday at 12:30 P.M., from the Clinicopathological conferences and from the monthly Staff meeting

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

Subscription rate is $3.00 per year. Those interested make checks payable to "Clinical Proceedings Dept.," The Children's Hospital, Washington, D.C. Please notify on change of address.

Copyright 1958, Children's Hospital

Entered as second class matter November 21, 1946 at the post office at Washington, D.C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

THE RENAL OSTEODYSTROPHIES

James A. Davis, Jr., M.D.*

Among the reasons why renal pathology in infants and children must be recognized early is the frequent relationship of renal disease to dwarfism, rickets, and other osseous defects which are preventable.

The following case illustrates the interrelationship of the genitourinary and skeletal systems with growth and development.

CASE REPORT

H. P., a 1 year old colored boy was admitted to Children's Hospital on July 2, 1955 because of anemia and severe acidosis without any obvious cause.

Past history revealed that this child was the product of a normal pregnancy, labor, and delivery; his weight at birth was 6 pounds, 4 ounces. Despite adequate dietary and vitamin intake and regular medical supervision he was admitted to another hospital at the age of 4 months because of malnutrition associated with an unexplained acidosis and fever; he also had club feet which had been treated previously by intermittent casting. Following the initial hospitalization he had been fairly well until the present admission.

Family history was negative for osseous, renal and endocrine disorders. On physical examination at admission he was a very poorly nourished and developed, listless, irritable colored boy who looked critically ill. Respirations were 70 per minute and of the Kussmaul type; his weight was 10½ pounds, his rectal temperature 99.8 degrees. There was moderate generalized pallor, slight dehydration, and prominent costochondral beading. The rest of the physical examination was normal except for a systolic blood pressure of 130–140 recorded while he was crying; his pulse rate was not remarkable.

On admission his blood hemoglobin was 7.0 gm. per 100 ml., and hematocrit 24 per cent. There were 16,000 leukocytes per cu. mm. with a slight shift to the left; moderate anisocytosis was demonstrable on smear.

Admission urinalysis revealed a hazy acid urine which was packed with white blood cells and contained 100 mg. per 100 ml. of albumin; the remainder of the urinalysis was normal but there was insufficient urine for specific gravity determination.

Chest x-ray on admission revealed the aforementioned costochondral beading and an increase in bronchovascular markings.

When the patient was admitted his blood carbon dioxide combining power was 9 volumes per 100 ml.; treatment with an intravenous solution of ⅙ M sodium lactate was begun immediately and resulted in marked improvement in the patient's condition. On the day after admission the carbon dioxide combining power had increased to 28 volumes per 100 ml., serum chloride was 98 mEq. per liter, and the serum calcium and phosphorus were 7.5 mg. per 100 ml. and 10.6 mg. per 100 ml. respectively. A blood transfusion was then given.

Several days after admission the child's bladder was found to be distended, and 100 cc. of residual urine was obtained almost immediately after voiding. At this time

---

* Former Chief Resident in Pediatrics, Children's Hospital.

his blood urea nitrogen was 48 mg. per 100 ml. Other blood chemical studies revealed: calcium 7.2 mg. per 100 ml., phosphorus 8.5 mg. per 100 ml., alkaline phosphatase 1 Bodansky unit, serum sodium 140 mEq. per liter, and serum potassium 5.6 mEq. per liter. During this period the boy was running a low grade fever, and vomited after ingesting food.

On July 7, 1955 an excretory urogram demonstrated no visualization of the renal calyces, pelves, or ureters. X-rays of the long bones revealed no definite evidence of rickets but the general architecture suggested a disturbance in calcium metabolism.

On July 8 a urine culture grew *E. coli* sensitive to chloramphenicol and nitrofurantoin. Despite several weeks of therapy with these drugs, and the use of an indwelling urethral catheter *E. coli* continued to be cultured from the urine.

A transurethral resection of the bladder neck was performed on July 27, for fibrous elevation of the median bar diagnosed at cystoscopic examination. The bladder was distended and had many diverticuli but no posterior urethral valve was found. For a few days following operation the child had a septic fever which gradually subsided to a low grade fever, unresponsive to treatment with various antibiotics for the remainder of his hospitalization.

The child's general condition deteriorated gradually throughout his hospital stay; at times he became markedly acidotic. In the face of severe anorexia, the maintenance of adequate nutrition, hydration and electrolyte balance necessitated the frequent use of parenteral fluids. He received five whole blood transfusions because of anemia during his hospital stay; there was never any evidence of bleeding or hemolysis. For acidotic episodes he was given either $\frac{1}{6}$ molar sodium lactate or 1.4 per cent sodium bicarbonate intravenously. Twice the usual dose of a vitamin concentrate was administered daily along with vitamin K because of the extensive use of broad spectrum antibiotics. In addition, 3 gm. of calcium gluconate was administered daily, either intravenously or orally.

The daily urine specific gravity was never above 1.015 and was usually below 1.010. The urine was usually acid and contained up to 400 mg. per 100 ml. of albumin. Almost all of the daily specimens contained pus cells in amounts usually recorded as "numerous" or "loaded". A few red blood cells were also occasionally seen.

The carbon dioxide combining power ranged from 20 to 30 volumes per 100 ml. The blood urea nitrogen gradually rose to 180 mg. per 100 ml. as renal impairment increased. The serum chloride was usually low, ranging from 75 to 101 mEq./L. Serum sodium was also usually low ranging from 116 to 145 mEq./L. Serum potassium ranged between 2.6 and 7.7 mEq./L. with hyperpotassemia predominating, and becoming a serious problem at one time.

For several days before death the patient's urine became scanty and resembled thick pus. He convulsed intermittently, vomited frequently, and finally died on September 7, 1955.

Postmortem pathological diagnoses were bronchopneumonia, chronic pyelonephritis, multiple kidney abscesses, hydroureters, diverticulum of the bladder, cystitis, congenital fibrous elevation of the median bar of the prostate, status postoperative transurethrotomy and renal rickets.

The kidneys were much reduced in size and irregular in shape. The capsules were tightly adherent to the roughened, nodular, light pink surfaces. The cortex and medulla were indistinct and the tissue was homogeneous and white. The ureters were dilated to 1.5 to 2.0 cm. in diameter. Microscopically many of the proximal and collecting tubules were dilated and filled with casts of acute inflammatory cells. Many of the glomeruli showed thickening of Bowman's capsule but the glomerular tufts were not remarkable. There were many abscesses throughout the parenchyma.

Grossly the skeletal system demonstrated a generalized broadening of the epiphyses, and the costochondral junctions showed marked beading. Microscopically, the epiphyseal cartilages were thickened, blood vessel invasion of the cartilage was markedly irregular, and thickened bony trabeculae radiated throughout the narrow uncalcified matrix surrounding them.

The parathyroid glands were not available for study.

DISCUSSION

Renal rickets, as the term implies, refers to any condition in which there is rickets secondary to renal pathology whether this be primarily anatomical or physiologic. As originally used, the term "renal rickets" applied only to conditions in which the kidney revealed abnormal histological changes of the whole functional unit, i.e., glomerulus and entire tubule. Now it is known that there are various other renal conditions, all basically different, which may also cause rickets. Because of this fact more suitable general terms have been applied to this group of diseases, such as renal osteodystrophy and osteonephropathy.

In general, there are six different types of disease entities in this overall group:

I. Classical renal rickets in which there is severe glomerular and tubular damage. Classical renal rickets may be caused by any of the following conditions: renal hypoplasia, congenital polycystic kidneys, obstructive uropathies, chronic pyelonephritis, or chronic glomerulonephritis.

II. The de Toni-Fanconi syndrome.

III. Hyperchloremic renal acidosis with or without nephrocalcinosis and/or nephrolithiasis.

IV. True vitamin D refractory rickets.

V. Idiopathic hypercalcuria.

VI. Primary hyperparathyroidism with severe secondary renal damage.

The osteonephropathies may also be classified as follows, depending upon whether the underlying renal pathology is congenital or acquired.

I. Congenital causes
   A. Primarily anatomical
      1. Renal hypogenesis
      2. Congenital polycystic kidney
      3. Obstructions in the genitourinary tract
         a) ureteropelvic
         b) ureterovesical
         c) enlarged median bar
         d) posterior urethral valve
         e) neuromuscular incoordination of the bladder neck
   B. Primarily functional
      1. The de Toni-Fanconi syndrome

2. Hyperchloremic renal acidosis
3. Idiopathic hypercalcuria
4. Vitamin D refractory rickets

II. Acquired causes
   A. Primarily anatomical
      1. Chronic pyelonephritis
      2. Chronic glomerulonephritis
      3. Renal damage secondary to primary hyperparathyroidism
   B. Primarily functional
      1. Idiopathic hypercalcuria (Staphylococcal renal infections may possibly be the cause of this condition).

In any of the osteonephropathies the findings in the osseous system depend upon several factors, e.g., the nature, extent, and duration of the renal lesion, and the age of the patient at the onset of the renal pathology. Naturally, if the renal pathology is extensive and chronic in a patient who is young and growing, there will be manifest bony involvement. If the renal disease is so severe that the patient dies before it has had a chance to produce its chronic effect upon the skeletal system, then obviously, bony involvement will be absent or minimal. If the renal pathology is mild, even though chronic, there may be only a chemical rickets or osteomalacia, or there may be a late developing mild rickets; after puberty, osteomalacia but not rickets may develop.

PATHOGENESIS OF BONE CHANGES

In some of the osteonephropathies, in addition to renal and osseous involvement, there may also be parathyroid gland involvement, the degree depending upon the nature, extent and duration of the imbalance in calcium and phosphorus metabolism. This parathyroid involvement takes the form of a compensatory increased functioning of the glands in an attempt to correct the deranged calcium and phosphorus metabolism. This compensatory action may be orderly, as is seen with most of the osteonephropathies, or it may be toxic, and cause marked disturbance of calcium and phosphorus metabolism as is seen with the extensive glomerular and tubular damage occurring in severe chronic glomerulonephritis. In this latter type of toxic secondary hyperparathyroidism there is a direct pathological effect upon bone which is not seen in the more orderly type of parathyroid overactivity. Metastatic calcification of various organs of the body, primarily kidneys, medium sized arteries and skin and subcutaneous tissues, frequently occurs with this toxic type of secondary hyperparathyroidism.

Rarely in patients with renal rickets of the classical type, pathological changes have been found in the pituitary gland. Whether there is any relationship between these changes and those in the parathyroid glands remains to be established.

The osseous changes in the osteonephropathies as observed roentgenologically are of two types: 1) rachitic changes, and 2) changes associated with secondary toxic hyperparathyroidism. If there is severe glomerular and tubular damage as in classical renal rickets both types may occur together. If there is primarily tubular damage and dysfunction, the rachitic picture will predominate. If, in the presence of severe glomerular and tubular damage, compensatory hyperparathyroidism elevates the serum calcium sufficiently to correct the rachitic process, there is increased bone destruction resulting in great part from the secondary hyperparathyroidism.

The early stages of the rachitic process cause rarefaction and fraying of the epiphyseal plate, and cupping of the metaphyses of the long bones. As the condition progresses the uncalcified metaphyses become invisible with resultant increase in the space between the visible end of the shaft and the epiphyseal ossification center. The shaft becomes rarified and the cortex thinned. These x-ray findings cannot be differentiated from those typical of the ordinary type of vitamin D deficient rickets although histologically the resemblance is not complete.

The skeletal changes of secondary hyperparathyroidism are usually seen only in the classical type of renal rickets (with severe glomerular and tubular damage), but may be seen in primary hyperparathyroidism with secondary severe renal damage due to metastatic renal calcification. Roentgenographic findings in secondary hyperparathyroidism occurring as a result of classical renal rickets may include solitary or multiple bone cysts (especially in the metacarpals), a coarse trabecular or "grainy" type of generalized decalcification, and subperiosteal bone resorption (primarily in the phalanges of the hands, especially the middle phalanx, but also in the upper one-third of the tibia, the distal one-third of the clavicle, and the distal ends of the ulna and radius). This subperiosteal bone resorption may have either a lace-like appearance or a ragged spicule-like appearance. Subperiosteal bone resorption and loss of the lamina dura around the roots of the teeth may be seen in either primary or secondary hyperparathyroidism.

Compensatory hyperparathyroidism is thus one mechanism causing some of the bone changes in renal rickets. This same mechanism, coming into play to a lesser extent in some of the other osteonephropathies, helps to regulate calcium and phosphorus metabolism without producing any of the typical x-ray changes of pronounced secondary hyperparathyroidism. Whenever the calcium level falls below the normal values of 9 to 11 mg. per 100 ml, there is a compensatory effect of the parathyroid glands to elevate it to normal. The parathyroid gland does this by causing calcium to be mobilized from bone; at the same time the parathyroid glands cause the blood phosphorus to be lowered by decreasing its tubular reabsorp-

tion. In the classical type of renal rickets, phosphorus in the serum cannot be effectively lowered because of the glomerular insufficiency which prevents its adequate filtration, however, the serum calcium can be elevated to levels even above normal. Additional dietary calcium and/or vitamin D may raise the serum calcium still further.

Other factors in the production of the bone disease are many, i.e., acidosis, phosphate excretion into the gut in severe glomerular and tubular damage, possibly pituitary gland lesions, the concentration of calcium and phosphorus in the blood, the availability of vitamin D, and the effect of renal disease itself on general nutrition.

Normally, bone resorption and deposition are going on all the time; bone salt is deposited in the form of a substance called dahlite. Serum acidosis occurring as a result of renal insufficiency increases bone resorption; in fact, anything which lowers the calcium ions, phosphorus ions, or carbonate ions to even a little below normal levels will cause increased bone resorption. On the other hand, it ordinarily requires a marked lowering of the calcium ion and phosphorus ion product to inhibit calcification, i.e., dahlite deposition.

Phosphate excretion into the gut occurs as an alternate route of phosphate excretion when the damaged kidney cannot adequately excrete phosphorus. Because of the increased amount of phosphorus in the gut there is assumed to be an interference with calcium absorption, possibly by formation of insoluble calcium phosphate.

Some authorities feel that there is a primary single congenital pituitary gland disturbance causing the dwarfism, infantilism and polyuria. However, very few cases of renal rickets reveal any pituitary pathology at autopsy.

If vitamin D is available in sufficient quantity to keep the serum calcium elevated it will tend to aid calcification and prevent rickets. More than the usual dose for normal children must be given to children with renal rickets until the rickets is healed.

Irrespective of the acidosis and disturbance in calcium and phosphorus metabolism, renal disease in itself can cause a deleterious effect on bone growth, probably due to loss of protein and retention of certain waste products by the kidney.

CLINICAL FINDINGS

The presenting symptoms of classical renal rickets depend upon the stage of the disease. The usual initial complaint is dwarfism, or failure to gain weight or grow. There may be obvious deformities such as rachitic rosary, genu valgum and frontal bossing, there may be polyuria and polydypsia, there may be a moderate to marked anemia, and there may

be signs and symptoms of acidosis. In the older child there may be sexual infantilism.

Physical examination will usually confirm growth failure. There may be a visibly or palpably distended bladder if a low urinary tract obstruction is present. Hypospadias or any abnormality of the external genitalia may be noted, and if present should always make one consider the possibility of another anomaly within the genitourinary tract.

LABORATORY FINDINGS

Examination of the blood will confirm the presence of anemia; a leukocytosis with a shift to the left will be found frequently in the face of complicating urinary tract infection.

Routine urinalysis usually reveals hyposthenuria, albuminuria, casts, a few red blood cells and usually an increased number of white blood cells; frequently, there is also acetonuria. Impairment of phenolsulfonphthalein excretion is usually noted.

Blood chemistries indicate retention of urea nitrogen, creatinine, uric acid, and sulfates. Potassium may also be retained to the point of dangerously high blood levels. The blood chlorides are usually low as is the serum sodium and the plasma carbon dioxide combining power. The serum phosphates are elevated due to abnormal retention and the serum calcium is initially low as compensation for the high serum phosphorus. The serum calcium may be raised to normal (or at times even above normal) by any of four ways, 1) increased calcium in the diet, 2) increased vitamin D in the diet, 3) compensatory action of the parathyroid glands, or 4) the administration of alkalinizing solutions. Serum alkaline phosphatase is frequently elevated. Another cause of initially low serum calcium is that calcium as a base, is lost in the urine along with sodium and other cations in order to help neutralize acid radicals which the damaged kidney cannot handle well. [In the cells of the distal tubules the enzyme, carbonic anhydrase, produces carbonic acid from carbon dioxide and water. The carbonic acid is then ionized to H^+ and HCO_3^- within the tubular cell. The hydrogen ion then passes through the cell membrane into the lumen of the tubule where it replaces a sodium ion in Na_2HPO_4 (i.e., disodium or basic phosphate) to form NaH_2PO_4 (i.e., monosodium or acid phosphate) which is excreted in the urine. The sodium ion thus conserved then enters the cell of the distal tubule and unites with the HCO_3 to form $NaHCO_3$ which is absorbed into the blood stream. In classical renal rickets this mechanism is interfered with, i.e., the ability of the tubule to manufacture H^+ is impaired. There is also a deficiency in NH_3^+ production by the damaged tubules. Therefore, two valuable mechanisms for excreting an acid urine are interfered with, necessitating the excretion of cations such as Ca^{++}

and Na^+ as substitutes for the lack of H^+ and NH_3^+. This mechanism of fixed base loss is one reason for the acidosis of classical renal rickets. Another reason is the retention of acid radicals. Because of this latter factor the acidosis in classical renal rickets can never be completely repaired by the replacement of the lost base alone.

Roentgenograms usually show evidence of bone lesions as previously discussed. Flat plate of the abdomen may rarely reveal metastatic calcifications in the kidneys. There may also be calcification in other tissues of the body, especially the medium sized arteries; the bones may even show evidence of osteosclerosis in certain areas. If renal function is severely impaired, intravenous urography will be worthless; there may however, be enough function remaining to reveal the location of a genitourinary tract obstruction. If intravenous urography is not successful, retrograde cystography and urography should be used in an attempt to demonstrate any etiological factor.

TREATMENT

Treatment of classical renal rickets is directed primarily at correcting the underlying renal pathology, where possible, before irreparable renal damage has taken place. Surgery offers the best hope for the obstructive uropathies; if performed early enough, renal function may be restored to normal or near normal. Where chronic infection is playing the primary role, the infection should be controlled as adequately as possible. In the case of congenitally hypoplastic kidneys or polycystic kidneys, little can be done. However, regardless of the nature of the renal lesion there are certain supportive measures which should be carried out, i.e., the administration of alkalinizing solutions, the administration of extra dietary calcium and vitamin D and the correction of the anemia with blood transfusions.

An alkalinizing solution which is recommended is Shohl's solution, (98 gm. of sodium citrate and 140 gm. of citric acid made up to a liter with water), administered daily in three or four divided doses for a total of up to 50 to 100 cc. per day, depending on the amount necessary to correct the acidosis. The citrate is metabolized after absorption, leaving the sodium free to help repair the deficit of sodium and also to help in the excretion of a less acid urine. The citric acid acidifies the gastrointestinal tract and thus aids in the absorption of calcium. Because of the increased blood pH due to alkalinizing solution, calcium ionization is depressed and may lead to tetany if additional calcium is not given initially.

Extra calcium should be administered until the total body deficit of calcium has been repaired as evidenced by the healing of the osseous

lesions. This usually requires at least two months of treatment. Vitamin D increases the absorption of calcium and phosphorus from the bowel and also increases the reabsorption of phosphorus from the urine. However, massive doses of vitamin D used in vitamin D refractory rickets usually cause a decreased reabsorption of phosphorus by the renal tubule; an effect similar to that of parathormone.

When the bone lesions have been repaired, alkalinizing solutions should be continued, but only the normal daily requirement of calcium and vitamin D should be administered since therapeutic doses of these substances may cause hypervitaminosis D or metastatic calcifications.

The resistant anemia of classical renal rickets is probably due to the depressant effect on the bone marrow of the elevated nonprotein nitrogenous products, plus the deleterious effect of renal disease on nutrition. It can be corrected only temporarily by repeated blood transfusions. Other measures such as iron, liver, folic acid and vitamin B_{12} are of no avail.

Hyperkalemia must be guarded against. If hyperkalemia develops it may be treated successfully at times by the cautious intravenous administration of glucose and regular insulin (1 unit of insulin for every 1 to 1.5 gm. of glucose). The utilization of glucose in this manner causes some of the potassium to enter the body cells from the extracellular fluid compartment thus lowering the serum potassium.

Prognosis in classical renal rickets depends on the nature, extent, and duration of the renal pathology and on the age of the patient. In many cases in which the renal disease is not too severe, treatment will reverse the bony pathology and re-establish normal growth for a while but the child may eventually die of progressive renal failure complicating urinary tract infection or intercurrent respiratory infection. In general, the prognosis for life in classical renal rickets is very poor.

DE TONI-FANCONI SYNDROME

The de Toni-Fanconi syndrome, as seen in childhood, is a recessively inherited renal osteodystrophy in which tubular dysfunction results in dwarfism and rickets. The basic defect is thought to be a deficiency of the enzyme phosphatase in the proximal tubules leading to inadequate phosphorylation and therefore insufficient reabsorption of amino acids, glucose and phosphates. Frequently, with this condition there is polyuria and polydypsia, anorexia, incidental respiratory and urinary tract infections, mild anemia, and a peculiar fluctuation of the body temperature from normal to both hypo and hyperthermic levels even in the absence of infection.

In this syndrome all twenty of the common amino acids except trypto-

phane and lysine may be found in the urine in abnormal amounts plus a few uncommon amino acids such as citrulline. The excretion of amino acids containing hydroxyl groups is increased out of proportion to that of the other amino acids. The blood level of amino acids is not elevated, and the hyperaminoaciduria is independent of the clinical state of the patient and the protein intake. One investigator found a direct relation of the hyperaminoaciduria to the glycosuria but not to the phosphaturia. This same investigator found that the amino acids constitute about 82 per cent of the total organic acids excreted and that the remainder are composed of lactic acid (11 per cent) and beta hydroxybutyric acid (7 per cent). The excess of the latter reflects the ketonemic response to hypoglycemia resulting from renal glycosuria.

The kidneys' ability to handle this increased acid load is overtaxed despite an increased ammonia production. Thus, there is a drain on basic ions in the serum, especially calcium, sodium and potassium. These cations are then drawn from their reservoirs in order that the chemical equilibrium of the blood will not be too greatly disturbed. This in turn results in a total body base depletion, leading to the acidosis which is usually found in the Fanconi syndrome. The calcium loss from the bones over a long period of time and the hypophosphatemia resulting from the hyperphosphaturia result in rickets which on X-ray is indistinguishable from vitamin D deficient rickets but which is different histologically. Due to the failure of cartilage cells in the epiphyseal plate to become calcified there is eventually a failure of cartilage cells to proliferate and thus a failure of skeletal growth resulting in dwarfism.

The hypocalcemia causes a mild degree of secondary hyperparathyroidism insufficient to produce cyst formation in bone or subperiosteal bone resorption; it merely tends to elevate the blood calcium level to normal or near normal.

The renal glycosuria occurs in the presence of a normal or slightly lowered blood glucose level. An abnormality in carbohydrate metabolism is shown by a wide variation in the fasting blood glucose tolerance curve. Fasting levels may be normal or subnormal but reach high peaks as in the diabetic. Epinephrine administration also causes a marked secondary rise. However, if a patient has previously been diagnosed as having this syndrome, neither the glucose tolerance curve nor the response to the injection of epinephrine should be studied since severe reactions and even death have occasionally followed such tests. These abnormalities of carbohydrate metabolism plus the occasional occurrence of an enlarged liver, cirrhosis, occasional jaundice, and the lability of the body temperature all suggest the involvement of some hepatic factor in the Fanconi syndrome.

Blood characteristics include mild anemia, normal or slightly lowered serum calcium, low serum phosphorus, low carbon dioxide combining power, low serum chloride, elevated alkaline phosphatase, and a tendency to low serum sodium and potassium. There may be signs and symptoms of hypokalemia, and the serum calcium may be low enough to produce tetany.

Glycosuria may be intermittent. As already mentioned there is a hyperaminoaciduria and a hyperphosphaturia. The reaction of the urine is usually fixed at a neutral or slightly alkaline pH, but it may occasionally be acid. This relative fixation of reaction occurs even in the face of the systemic acidosis, and it is probably due to an over production of ammonia by the renal tubules, since the amonia-nitrogen coefficient in the urine is usually increased. When corrected for the presence of albumin and sugar the specific gravity is relatively fixed. There is a high ratio of amino acid nitrogen to total urinary nitrogen (about 10 per cent as compared to 1 to 2 per cent normally).

Roentgenologic studies usually are of value only in demonstrating the rickets and ruling out anatomical abnormalities of the urinary tract which are not typically a part of the Fanconi syndrome.

Histologically, the kidneys show primarily tubular changes with little or no glomerular abnormalities early in the disease. Later there may be severe glomerular damage however, as a sequel to cystine deposition in the kidney or possibly due to continued passage of excessive amounts of organic acids or other substances. One author feels that it is possible to explain the congenital tubular dysfunction on the basis of a congenital structural anomaly of the proximal tubule, which he describes as shorter than normal and joined to the glomerulus by a narrow swan-like neck which is lined with regular low cuboidal epithelium instead of the columnar epithelium usually seen. None of these changes has been found in diseases other than the Fanconi syndrome. This same author feels that because of the inadequacy of the proximal convoluted tubule there may be a saturation of the reabsorptive mechanism for amino acids at unduly low levels. The distal tubule often contains casts of epithelial atrophy. These distal tubular changes are found infrequently and may be a late result of the long continued action of an unidentified substance in its passage down the nephron. Interstitial fibrosis may result from the seepage of material from the lumen through the inadequate tubule into the interstitial tissue.

CYSTINOSIS

Cystinosis is thought by many to be closely related to the Fanconi syndrome since some cases of Fanconi syndrome have cystinosis. However,

each syndrome is often seen without evidence of the other. Cystinosis is a pathological condition in which cystine deposits are found in almost all organs of the body, especially reticuloendothelial system and kidneys. Cystinosis may be diagnosed by finding cystine crystals in the bone marrow and in the cornea. In general, patients with cystinosis do not have cystinuria and vice versa. In the Fanconi syndrome without cystinosis there may be an excretion of cystine proportionate to that of the other amino acids excreted, or there may be an abnormally high excretion of cystine.

Treatment of the Fanconi syndrome is directed primarily at correcting the acidosis and healing the osseous lesions. The acidosis is corrected by the oral administration of Shohl's solution in a dose sufficient for the individual case. If there is a tendency to hypokalemia, potassium citrate should be used with the sodium citrate. Additional calcium is added to the diet along with high doses of vitamin D, until the rickets is corrected roentgenographically. The long range results of treatment are not gratifying even though the rickets and acidosis are correctible, for the eventual outcome is usually death from severe acidosis or renal failure.

One investigator has suggested using tocopherol in the treatment of cystinosis. He found that it caused a decrease in the cystine deposits in the cornea and helped also to lower the blood urea nitrogen. Tocopherol is a biological antioxidant and was used in an effort to prevent or decrease oxidation of cysteine to cystine. However, the real value of tocopherol, if any, remains to be proven or disproven by further clinical trials.

HYPERCHLOREMIC ACIDOSIS

A third type of renal osteodystrophy is the entity known as the Butler-Albright syndrome or hyperchloremic renal acidosis with or without nephrocalcinosis and nephrolithiasis. This syndrome is due to a tubular dysfunction in which there is an inability of the distal tubule to produce enough hydrogen ions to secrete an acid urine, coupled with a deficient ammonia production by the tubule. Both of these deficiencies therefore, result in an acidosis of renal origin. The hyperchloremia results from two causes: first, as a compensatory mechanism for the low carbon dioxide combining power which results from the kidneys' inability to secrete an acid urine, and second, probably from a selective increased reabsorption of chloride by the tubule.

The clinical picture in this disease is one of rickets, dwarfism, polyuria, occasionally fractures, weakness and the characteristic signs and symptoms of potassium deficiency occasionally resulting in death. There may also be nephrolithiasis and/or nephrocalcinosis. Acidosis is an essential feature. Occasionally tetany or renal colic may be the presenting symptom.

The basic defect is thought to be a deficiency in the distal tubule cells of the intracellular enzyme, carbonic anhydrase, which synthesizes carbonic acid from carbon dioxide and water and then ionizes the acid to H^+ and HCO_3^-. The hydrogen ion is then incorporated into the previously explained phosphate system and the sodium ion thus spared enters the cell and joins the bicarbonate HCO_3^- ion. Because of failure of this mechanism there is a low bicarbonate plasma fraction, and also a depletion of plasma base since the sodium ions are not saved. Thus, the defect here is thought to be the same as the tubular defect in the classical type of renal rickets. Another mechanism for acidifying the urine is also defective in this syndrome. There is defective ammonia production which may be due directly to tubular disease via a deficiency of the enzyme glutaminase or may be secondary to low urinary acidity produced by the basic defect in the formation of hydrogen ions already mentioned. Urine alkalinity in itself will reduce ammonium production and increase the excretion of bicarbonate ion with fixed base.

Pathologically there may be degenerative changes in the tubules. The convoluted tubules may be dilated, and the tubular epithelial cells swollen, finely granular and vacuolated; the tubular cells have at times shown small foci of papillary overgrowth. Usually the glomeruli are normal but occasional glomeruli may be scarred or atrophied. There may be gross calculi in the renal pelvis and/or small macroscopic or microscopic deposits of calcium in the renal parenchyma, usually in the pyramids. The alkalinity of the urine, plus possibly a functional insufficiency of the reabsorbing mechanism for urine calcium, both favor the precipitation of insoluble calcium phosphates. There may be no calcium deposition (nephrocalcinosis) however, for this is not an essential feature of the syndrome.

Laboratory examination of the blood reveals a low plasma carbon dioxide combining power, an elevated serum chloride, markedly subnormal serum phosphate, slight reduction of serum calcium and increase in alkaline phosphatase. Blood urea and non-protein nitrogen are not usually elevated. There may be an elevation of the total plasma electrolytes due to the increased reabsorption of chlorides from the renal tubules with an incidental increased reabsorption of fixed base which may partially offset the loss of base in the urine. Initially, calcium is the principal cation lost in the urine. This loss of calcium from the bones continues until the calcium reserve is sufficiently depleted so that potassium must then be withdrawn from the body cells. This potassium loss may lead to clinical evidence of hypokalemia while the calcium loss leads to rickets. Because of the lowered serum calcium it is felt that there is a mild degree of secondary hyperparathyroidism which causes the serum calcium to

be elevated toward normal and the serum phosphorus to be depressed by way of urinary loss through the usually intact glomeruli.

The calcium and phosphorus content in the urine are markedly increased. Total base excretion is high. There is a low fixed hydrogen ion content, a low fixed specific gravity, low ammonium content, and usually a polyuria which is not affected by pitressin. Albuminuria is seen frequently but occurs in the absence of evidence of glomerular dysfunction. Phenolsulfonphthalein excretion is usually normal. The chloride output of the urine varies from a trace to considerable amounts, apparently depending on the body intake of chlorides. The low specific gravity which is not invariably present, appears to be due to failure of water reabsorption in the distal tubule. This leads to polyuria, polydypsia, and at times to moderate hemoconcentration.

As in the Fanconi syndrome there is not enough secondary hyperparathyroidism to produce the bone changes of toxic glandular hyperactivity. Consequently, on roentgenologic examination of the skeleton, only rickets and dwarfism are noted. Here, too, as in the Fanconi syndrome the rickets is indistinguishable on X-ray from ordinary vitamin D deficient rickets. X-ray examination of the abdomen will sometimes reveal nephrocalcinosis and/or nephrolithiasis, although the former may be present and detectable only on histological examination. The renal radiodensities seen in this condition are usually in the renal medulla, as opposed to those which may occasionally be seen in the renal cortical areas in metastatic calcification occurring in the classical type of renal rickets.

The results of treatment of this type of renal acidosis, if started early in life, are more gratifying than that of the Fanconi syndrome. Proper therapy consists in the administration of an alkalinizing solution such as Shohl's solution orally in quantities sufficient to compensate for the loss of excessive base in the urine. In addition, extra vitamin D and calcium should be given only until the rickets is completely healed; following healing, these substances should be given in amounts equal to the normal daily requirement for a child of the same age. Salt should be restricted to reduce the hyperchloremia, and thus help to correct the acidosis. However, since the basic deficiency of carbonic anhydrase still exists, the plasma carbon dioxide combining power remains relatively low. Treatment also has no effect on the polyuria. However, the rickets heals, growth is restored when the epiphyses have not already united, and there is an improvement in strength and general health. There is frequently a diminution of the nephrocalcinosis and nephrolithiasis. However, if treatment is not instituted early enough there may be so much calcium deposition in the renal parenchyma as to produce glomerular damage; in such a situation, a picture closely resembling the classical type of renal

rickets appears. In the treatment of the uncomplicated case of hyperchloremic acidosis the child's blood electrolytes and urine calcium content should be checked frequently to determine any change in the need for alkalinizing solution. Sulfonamides should be avoided in this condition since they further interfere with the carbonic anhydrase mechanism.

IDIOPATHIC HYPERCALCURIA

Idiopathic hypercalcuria is another condition capable of producing rickets. Excessive calcium is excreted due to inadequate tubular reabsorption of this ion from the glomerular filtrate regardless of the level of serum calcium. Normally, when the serum calcium falls below 7 mg per 100 ml. no calcium is excreted in the urine. Here, however, calcium is not adequately reabsorbed even at lower serum levels. The resultant hypocalcemia causes a mild secondary hyperparathyroidism which elevates the serum calcium toward normal and tends to lower the serum phosphorus. The sequence of events in the disordered homeostasis of idiopathic hypercalcuria is, therefore, the same as that occurring in vitamin D deficient rickets except that the first step is increased calcium excretion rather than decreased calcium absorption. Because of the increased calcium excretion renal calculi are formed, especially if there is a disproportionate increase in the hypercalcuria produced by an acid ash diet or excessive vitamin D administration. Calculi are more common and rickets less common in this condition than in hyperchloremic renal acidosis. In the majority of cases of idiopathic hypercalcuria there is only a chemical osteomalacia without a high alkaline phosphatase; rarely there may be definite bone changes.

The treatment of this condition if osseous changes are present, is a high vitamin D, high calcium diet. This therapy is contraindicated however, if nephrolithiasis is present. It has not yet been established whether staphylococcal pyelonephritis which is a relatively frequent complication of idiopathic hypercalcuria is the cause or the result.

REFRACTORY RICKETS

A fifth condition in which rickets is found in association with renal dysfunction is known as vitamin D refractory rickets. This is a hereditary condition in which there seems to be an abnormally high renal clearance of phosphorus due probably to decreased reabsorption by the renal tubule. This results in hypophosphatemia in all untreated cases. The hypophosphatemia is associated with a normal serum calcium level in some cases; in other instances, hypocalcemia and tetany occur. The reason for the occurrence of hypocalcemia in this disease has not been definitely established. The alkaline phosphatase is abnormally high in all untreated cases.

Rickets, roentgenologically similar to vitamin D deficient rickets, usually develops during the first year of life if only the usual amount of vitamin D is administered. Severe deformities may result.

Treatment consists of the administration of large amounts of vitamin D in doses ranging from 5,000 to 1,000,000 units daily. Initially, 50,000 units are tried and results are interpreted on the basis of monthly X-rays. Serum calcium and phosphorous determinations should be obtained at monthly intervals until they are stabilized and then once every two to four months. A closer check can be kept on the results of therapy by grossly determining calcium excretion in the urine (Sulkowitch test) two or three times weekly. If the Sulkowitch test is consistently 4+ the serum calcium should be checked. If hypercalcemia is present the dose of vitamin D should be reduced. Although the rickets heals, the serum phosphorus level rarely returns to normal. Once deformities have developed they must be treated by orthopedic measures. Orthopedic correction of deformities should not be attempted prior to healing of the rickets (this applies to all of the osteonephropathies), and when immobilizing procedures are used the patient should be carefully observed for evidence of hypercalcemia and hypercalcuria. Deformities can be prevented if adequate treatment is instituted early.

HYPERPARATHYROIDISM

The sixth condition in which rickets and dwarfism may be associated with renal impairment results from renal damage secondary to idiopathic hyperparathyroidism. This condition is rare in childhood, and, as in the adult, has as its primary etiological factor an idiopathic hyperfunctioning of the parathyroid glands due to adenoma, or hyperplasia or hypertrophy of glandular tissue. The resultant hypercalcemia may at times cause metastatic calcification in the kidneys severe enough to cause extensive tubular and glomerular damage; this may produce a clinical picture almost identical to that of classical renal rickets with secondary hyperparathyroidism. Treatment is directed primarily at the idiopathic hyperparathyroidism. There must be surgical removal of enough of the tumor or of the hyperfunctioning parathyroid tissue to reduce the serum calcium to normal levels. In the presence of severe renal damage more parathyroid tissue should be left intact to maintain a normal calcium level than would be required in a case in which there is little or no renal damage. Once the hyperfunctioning parathyroid tissue has been removed, management of the patient is along the same lines as that of classical renal rickets with severe glomerular and tubular damage.

In conclusion it may be said that whenever rickets and dwarfism occur

in childhood, renal damage and/or dysfunction must be strongly considered as a possible etiologic factor. If the correct diagnosis is made early in life it is possible to correct the rickets and dwarfism in some cases. On the other hand, chronic renal disease, or any condition capable of producing it must be considered as a potential cause of future osseous disease and should be treated accordingly even if the skeletal system has not yet been noted to be involved.

BIBLIOGRAPHY

Anderson, D. H., and Schlesinger, R. R.: Renal Hyperparathyroidism with Calcification of the Arteries in Infancy. Am. J. Dis. Child., **63:** 102, 1942

Anderson, I. A., Miller, R., and Kenny, A. P.: Osteomalacia and Renal Glycosuria in Adults; Metabolic Investigation of Case with Particular Reference to Its Relation to Fanconi Syndrome and to Treatment. Quart. J. Med., **21:** 33, 1952.

Albright, F., and Reifenstein, E. G., Jr.: Parathyroid Glands and Metabolic Bone Disease. Williams and Wilkins Company, Baltimore, 1948.

Bickel, H., and Smellie, J. M.: Cystine Storage Disease with Amino-Aciduria; Preliminary Communication. Lancet, **1:** 1093, 1952.

Brown, R. J. K.: Clinicopathologic Study of Cystinosis in Two Siblings. Arch. Dis. Childhood, **27:** 428, 1952.

Cancelmo, J. J., and Bromer, R. S.: Osteonephropathy in Children (with Special Reference to Renal Rickets and Nephrocalcinosis). Am. J. Roentgenol., **65:** 889, 1951.

Claireaux, A. E.: Renal Osteodystrophy. J. Path. & Bact., **65:** 291, 1953.

Clay, R. D., Darmady, E. M., and Hawkins, M.: Nature of the Renal Lesion in the Fanconi Syndrome. J. Path. & Bact., **65:** 551, 1953.

Dimson, S. B.: Fanconi Syndrome in Two Siblings. Proc. Roy. Soc. Med., **45:** 454, 1952.

Faber, H. K., Abramson, M., and Silverberg, R. J.: Butler-Albright Syndrome of Tubular Nephropathy, Acidosis and Late Rickets, Dwarfing, Diabetes Insipidus, and Nephrocalcinosis. Standard M. Bull., **6:** 157, 1948.

Hughs, B., and Gislason, G. J.: Osteonephropathy. J. Urol., **55:** 330, 1946.

Jackson, W. P. U., and Linder, G. C.: Innate Functional Defects of Renal Tubules with Particular Reference to the Fanconi Syndrome; Cases with Retinitis Pigmentosa. Quart. J. Med., **22:** 133, 1953.

King, F. P., and Lockridge, E. P.: Cystinosis (Cystine Storage Disease); Report of a Case, Chemical Isolation and Quantitative Determination of Cystine in Lymph Nodes, Spleen and Liver. A. M. A. J. Dis. Child., **82:** 446, 1951.

McCune, D. J., Mason, H. H., and Clarke, H. T.: Intractable Hypophosphatemic Rickets with Renal Glycosuria and Acidosis (The Fanconi Syndrome). Report of a Case in Which Increased Urinary Organic Acids Were Detected and Identified, with a Review of the Literature. Am. J. Dis. Child., **65:** 81, 1943.

Pugh, D. G.: Subperiosteal Resorption of Bone; Roentgenologic Manifestation of Primary Hyperparathyroidism and Renal Osteodystrophy. Am. J. Roentgenol., **66:** 577, 1951.

Rule, C., and Crollman, A.: Osteonephropathy; Clinical Considerations of Renal Rickets. Ann. Int. Med., **20:** 63, 1944.

Seward, W. H.: Renal Rickets. J. M. Soc. New Jersey, **48:** 464, 1951.

HEMANGIOMAS IN CHILDHOOD

Panel Discussion

Frederic Gerard Burke, M.D.,* Robert E. Moran, M.D.,† Naomi M. Kanof, M.D.‡

Dr. Burke:

Hemangiomas are a very common problem in the practice of pediatrics, and may affect possibly twenty-five per cent of all children. The chief problem is often the worried mother since the problem of the hemangioma is frequently glossed over by the physician, and the *lack* of importance or in some instances, the *great* importance of these lesions is not emphasized. This panel, therefore, will be presented from the point of view of the pediatrician who initially sees the hemangioma and has the experience of following the development and progress of the lesion, from the point of view of the surgeon who must operate on some of them, and from the viewpoint of the dermatologist who sees the group that never needs to reach the surgeon. The subject of hemangiomas was briefly and very well covered by Dr. Alfred Falk in the May of 1955 issue of the *Pediatric Clinics of North America*, and a good portion of my remarks are from this report.

The hemangioma is a benign tumor consisting of autonomously formed blood vessels and is usually classified into one of three categories. The first is the nevus flammeus or the port wine stain which is usually a unilateral lesion most frequently seen on the face, and frequently following the course of the trigeminal nerve. It ranges in color from faint pink to purplish-blue and is solely located at the skin level. These port wine stains and flammeus lesions are most commonly seen on the face and head and frequently on the nape of the neck.

The second type of hemangioma is the nevus vasculosus, or strawberry mark. It is about the treatment of this particular type of lesion that most discussion arises. This is a circumscribed tumor, elevated above the surface of the skin, usually reddish-pink to bright red in color, and frequently extends somewhat into the underlying corium.

The third type is the cavernous hemangioma which has a large component in the subcutaneous tissue but which is also frequently elevated above and involves the skin. This has a body and depth to it which can

* Attending Staff, Investigator, Research Foundation, Children's Hospital; Professor, Pediatrics, Georgetown University School of Medicine.

† Attending Staff, Children's Hospital.

‡ Associate Staff, Children's Hospital; Editor, Journal of Investigative Dermatology.

be felt, and frequently is contiguous with one of the larger blood vessels. The overlying skin may be normal in color or have a bluish discoloration. Mixtures of these three types of hemangiomas occur; these would form a separate fourth category of clinically classified hemangiomas.

The origin of these tumors is not fully understood, but they arise from mesenchyme, the source of vascular tissue, which gives rise to nests of angioblastic cells. These become separated from the blood vessels in ectopic areas, and are usually superficial to the main blood vessels. These nests of angioblastic cells coalesce, intercommunicate, and in turn connect to the general circulation via the afferent and efferent leads which eventually develop. Occasionally a hemangioma will have only an afferent lead; this type, since the blood has no way of returning to the circulation, grows and extends rapidly and requires prompt management in early life.

The cause of these benign tumors remains unknown. Among the theories which have been presented is the pressure on the involved part of the infant *in utero* by the bony prominences of the maternal pelvis. This is speculative, but there is certainly a predilection for these lesions to occur on the head; probably more than half of them occur in this location. Another favorite location is under the twelfth rib. These tumors are about twice as common in females as in males and are more frequently seen in the premature infant.

While hemangiomas are called birthmarks, and most textbooks describe the majority as being present at birth, this is not my own observation. In my experience, ninety per cent are not present at birth, but become visible sometime after the physician sees the infant in the hospital and declares everything to be normal. Then, sometime between the first and the fourth week of life, the hemangioma makes its appearance; it can, however, first appear anytime up to six or seven months after birth. Hemangiomas may be single or multiple.

Probably 25 per cent of all normal infants have a nevus flammeus over the glabella, over the eyelids, or over the naso-labial folds; this is particularly true of the blond, fair-skinned children. The nevus flammeus is so common that many of us, I am sure, fail to mention it to the parents. These nevi should, however, always be discussed because their location in a cosmetically important area makes them the source of considerable concern to many parents. In the early weeks, when the skin has little pigment and the infant is apt to be flushing at fairly regular intervals, these flame nevi are really quite prominent. To maternal eyes they are real defects. It must be explained that with thickening of the skin and development of further pigmentation, they gradually disappear from view. Occasionally one persists up to the age of six years in a fair-skinned

child and will be noticed when he gets angry or flushed. Another common location for flame nevi is at the nape of the neck and here the nevus tends not to disappear; developing hair, however, effectively covers it and it does not form any cosmetic basis for concern.

The nevus vasculosis, or strawberry mark, also grows at a rate paralleling the child's growth and occasionally faster when the efferent drainage does not equal the afferent blood supply. The parents should be warned of this, but be reassured that when the child's general growth pattern slows, as it does between the second and fifth year of life, there is a general tendency for these lesions to involute spontaneously. The first basis of treatment of the strawberry mark is, then to leave it alone; it should be observed at intervals, preferably photographed, and if it gradually begins to involute, should receive no therapy whatsoever.

Under certain conditions, however, when these lesions occur adjacent to vital structures the rate of growth and changing appearance should be made the object of repeated observations to determine any necessity for treatment. For example, deep lesions around and about the bones of an extremity may stimulate unilateral growth of that limb and result in considerable asymmetry of the arms or legs. Similarly, when these lesions are located around the eye, intraocular pressure on that side may increase and may even cause blindness in the particular eye. In addition, any hemangioma of this type may become necrotic and become infected, particularly on exposed parts of the body which are subject to trauma.

Cavernous hemangiomas may present peripherally as a small capillary mass without a vascular return and develop massive proportion below the skin with or without disturbance of other tissues or organ functions. They may also have no peripheral representation or appear as ropy tortuous vascular channels just below the skin. The rate of growth and positions are the important factors in determining treatment. These growths do occur internally and, of course, affect any organ, the liver, the spleen, the intestinal wall, the brain, and so on. The intestine and liver are not infrequent sites of spontaneous and active bleeding, and may form a basis for repeated and recurrent hemorrhage which may result in exsanguination.

In the differential diagnosis of hemangiomas, several other entities must be considered. The first of these is the nevus araneus, or the spider nevus, which is most commonly seen on the face but can be found in any location. This is a lesion which has a central, bright elevated blood vessel with fine radiating branches, and is, in effect, an arteriovenous fistula. A familial tendency to telangiectases, associated frequently with bleeding from the nose or intestine constitutes hereditary hemorrhagic telangiectasis.

Another skin lesion which may simulate or be misclassified as a hemangioma is the circinoid aneurysm, also known as the racemose type of hemangioma. This is also primarily a congenital arteriovenous fistula, and is a pulsating vascular tumor. It occurs usually in the area of the carotid artery and consists of a tangle of blood vessels capable of enlarging to the point of bone erosion.

The granulosa pyogenicum is a small, red, pedunculated skin nodule occurring usually at the site of previous trauma. This tumor is quite friable and bleeds easily. When surgically removed, it will be found to have newly formed capillaries and a pedunculated type of attachment to the dermis at the base, confirming the impression of very deep roots.

The presence of translucent vessels with a "cayenne pepper" appearing angiomatous studded surface is indicative of lymphangioma. Soft compressible masses having the appearance of normal skin are variants of the lymphangioma. When they occur in the axillary or supraclavicular area, they may constitute a cystic hygroma.

Finally, the angioma serpiginosum, a snake-like lesion, is an eruption which may contain angiomatous puncta. Involution of this lesion, with or without therapy, is usually slow and spontaneous, but frequently incomplete. Maligancies of blood vessels occurring in infants are of two types, the hemangiomatous sarcoma, and the hemangioma, endothelioma type. These are reported to consist of dark red, vascular masses having invasive and metastatic ability and frequently bleeding and ulcerating.

Five modes of therapy are available for treating hemangiomas. The first is, as previously mentioned, to leave them alone and observe them at regular intervals; the second is cryotherapy, or freezing with carbon dioxide snow; the third is radiotherapy of various types (thorium, X-ray, radium); fourth, injection with sclerosing materials; and lastly surgical excision. Occasionally, combinations of these treatments have to be used.

The nevus flammeus should best be left alone. For the more extensive, cosmetically disfiguring superficial lesions, sandpapering or tattooing has been recommended. Camouflaging with cosmetics has been a very successful method in many cases.

Spontaneous involution of the strawberry mark, as previously mentioned, also occurs frequently. The central area gradually becomes white (indicating a spontaneous necrosis of the blood supply to the lesion) and slowly fades. If this lesion grows at a faster rate than the normal growth of the child or if it is located in an area of cosmetic significance, other methods of treatment will, of course, have to be considered.

In the past, irradiation therapy of hemangiomas has been rather widely used. At the present time, however, both medical profession and lay public are sensitized to the hazards of radiation, with the result that this

method of management will probably become less popular in the future. Radioactivity, particularly in the very young, may produce effects which will not be apparent until some ten or twenty years later. New malignant growths may arise from the injured site that has been irradiated.

The stunting of a growth center is a very dear price to pay for the injudicious use of radiation therapy on a perfectly benign lesion. It is my belief that radiation therapy should be reserved for the very exceptional case, one that is not surgically accessible or one that does not permit correction by any other method. A further point is that the scars left by radiation therapy are frequently much worse than the original lesion. I have also seen several children who had loss of muscle mass in their extremities, when, as an infant, they had radiotherapy of a small hemangioma on the thigh or lower leg. With the passage of eight or ten years, the difference in circumference of the two extremities may be as much as two to three inches; a very unfortunate occurrence considering the benignity of the original lesion.

Cavernous hemangiomas should in the great majority of cases be treated by surgery, an occasional one probably benefiting from injection of sclerosing materials.

In summary, it should be mentioned that the great majority of commonly occurring hemangiomas will spontaneously involute, indicating that conservative management is the treatment of choice. The lesions should be evaluated at frequent intervals and are best observed by repeated photographs. Specific therapy should be reserved for those tumors which may cause future physical or social problems, and the decision should be rendered on the basis of the location of the hemangioma as well as the type.

Dr. Moran:

I would like to express my complete agreement with Dr. Burke on the generally good prognosis of these lesions without any treatment. Two years ago, Blackwell reported some 200 rather large hemangiomas of the capillary type to which he gave no treatment, but just observed. The great majority completely regressed after two to three years of age.

Why, then, is it necessary for us to treat them? The main reason is that some interfere with function. Any hemangioma of the eyelid that interferes with vision, any hemangioma of the nose that interferes with breathing, any hemangioma about the mouth which may be accidentally bitten, or any hemangioma occurring on a weight-bearing or other surface subject to enough trauma to cause ulceration should be treated. A second reason for removal is that instead of regressing the hemangioma con-

tinues to grow in size. My experience has not paralleled Dr. Burke's in observing that they follow the growth pattern. The capillary type either regresses or grows fairly rapidly.

Dr. Burke spoke of the three types of angiomas. I think we will have to include the arteriovenous fistulas with the cavernous hemangiomas because they have all of the pathology of the cavernous type. From my experience, arteriovenous fistulas are more common than we are usually led to believe.

For the port wine stains that do not regress, sanding may make them look better. It is best to try out only a small area at first, however, because we sometimes see as much scarring following sanding as we would if we had left them alone. When a port wine stain is smooth I think that a cosmetic covering is about as good as anything.

Now, although Dr. Burke is surely correct about X-ray irradiation, the Barrett Brown group in St. Louis does use small doses, a tenth of a millicurie (E) of radon seeds, with good results. Of course I have seen a nose the size of an infant in a young woman who had had a hemangioma of the nose treated by irradiation years before. And I have seen a bowed leg, four inches shorter than its partner resulting from a small dose of irradiation to a rather large cavernous hemangioma located just below the knee.

The simplest type of capillary hemangioma with a smooth skin and only faint discoloration usually fades out and needs no treatment. Some, however, do not fade, but with cosmetics can be perfectly disguised. Capillary hemangiomas with cavernous components extending into the subcutaneous tissue can also be left alone. If, however, they show signs of rapid growth, injection therapy and perhaps later surgery may be necessary.

Perhaps the most difficult hemangioma to treat is a cavernous hemangioma of the parotid gland since any surgery in this area is liable to injure permanently the facial nerve. Very small doses of radon seeds will frequently cause reduction in size. Sometimes injection of sclerosing solutions is of value. The general tendency is to be conservative and avoid surgery if possible.

Hemangiomas of the lip frequently ulcerate due to constant trauma. These do not respond well to radiation, or to injection. Surgical removal by an approach from the mucous membrane is probably best.

Some cavernous hemangiomas involve the entire thickness of the cheek including the oral mucosa, and may extend even to the tonsillar fossa. This type is best treated by injection with sclerosing fluids or boiling water.

Arteriovenous fistulas must be corrected by surgery, of course. They respond to no other form of treatment.

Capillary hemangiomas of the nose frequently grow rapidly. The nose is very sensitive to radiation as far as the growth of nasal cartilage is concerned and any irradiation of this area frequently results in a markedly deformed nose. These angiomas, therefore, may best be treated by injection or if possible, by surgical removal.

In some unfortunate children there are multiple cavernous hemangiomas with associated arteriovenous fistulas over a large portion of the body. When these are confined to one or more extremities there is marked over growth of the involved part due to the increased amount of blood in that area. These patients frequently have associated internal hemangiomas and may die of massive gastro-intestinal hemorrhage or bleeding into other visceral organs.

Hemangiomas occasionally act like malignant growths although they do not metastasize widely. Instead they may be locally malignant and act like melanomas by developing satellite lesions which may be surgically removed but frequently recur. The only satisfactory form of therapy is wide excision and rotation of a skin flap to cover the defect.

Ulceration of a hemangioma can be a real problem. A hemangioma that looks rather innocent may begin to break down leading to necrosis which may actually result in complete or partial sloughing of an ear, the tip of the nose, the lip, etc. Children with such angiomas frequently become electrolyte problems from fluid loss and should be treated exactly as if they had burns. Frequently the only thing that will stop the progress of the ulceration is very small dose of radiation done by an expert. These are many times desperate cases.

Another extremely difficult type of hemangioma to treat is the combination capillary-cavernous type which extends into the orbit with a resultant exophthalmus. Radiation around the orbit is hazardous, frequently results in blindness, and should not be used. Careful surgical extirpation with later plastic surgery to cover the defect offers best results. Hemangiomas of the orbit, *per se*, also occur. The preferred surgical approach to these is a lateral decompression and removal of the lateral wall of the orbit through an excision in the hairline.

Dr. Kanof:

First, I would like to say that I am substantially in agreement with the previous speakers. There is no problem in making a decision as to whether to treat a large hemangioma with a cavernous component. These we immediately refer to the surgeon for whatever treatment he deems

best. There is no problem with the nevus flammeus; we leave it absolutely alone. There is a problem with the capillary hemangiomas that do not really need therapy, and yet there is a reluctance not to treat them.

The parents of a patient who have watched their first child's lesion get larger and larger become apprehensive about the unesthetic appearance even though the lesion does not interfere with any vital structure. So when the lesion occurs in a subsequent child they are less tolerant of the "watch and wait" attitude and hurry to the pediatrician to get his permission for treatment. Hence from the point of view of the patient or the parent, no lesion is too small a lesion. They do not want to watch a lesion progress from one centimeter to two centimeters in diameter. They also demand pretty quickly, when it gets to be three centimeters, that something be done, but they are at the same time reluctant to subject a tiny infant to surgery.

What do we do about them? I seem to be alone, but I think that they are all worth treating. There is the danger that they may become cavernous. It seems injudicious caution not to treat them when with several applications of dry ice they will soon disappear. There is a chance, of course, that a scar will be produced, but the plastic surgeon can easily remove this when the child is older. You are buying time when the child is young; you are preventing extension of the growth. You may produce a scar but this will be no worse than the scar induced by the resolution of the hemangioma by itself, and this can be excised at a later date.

One word of caution, however: when I talk about cryotherapy (carbon dioxide snow) I do not mean destructive doses of cryotherapy. A destructive dose induces ulceration, infection and bleeding. The lesion should not be destroyed but instead must be treated with only small doses at repeated intervals. It should be irritated just enough to be permitted to regress by itself.

Ten years ago it was my opinion that one should never touch the port wine stain unless the surgeon thought he could get a good plastic repair. It is well known that anything that disturbs the surface, such as radium or cryotherapy leaves a terrible result. If left alone, it may at least be covered adequately with cosmetics. However, good results have been obtained occasionally in the treatment of nevus flammeus with Thorium X in infants and children. Delay in treatment is not prejudicial to the patient. Often one waits until early adolescence to start therapy. Thorium X should be effective within a limited number of treatments. If the lesion shows no sign of regression, therapy should be discontinued because then irradiation effects can be produced with no therapeutic gain.

CONGENITAL COMPLETE HEART BLOCK

Uberne Valerio, M.D.*

The diagnosis of congenital complete heart block was first made by Morquio in 1901. This condition is very rare; approximately 105 cases have been reported in the world medical literature. On twelve occasions the diagnosis has been made ante-natally.

The following case is a classical example of this rare entity.

CASE REPORT

J. W., a 3 month old colored girl, was born at the D. C. General Hospital on February 3, 1957 after forty weeks of uncomplicated pregnancy and spontaneous delivery. Birth weight was 5 pounds 8 ounces.

At birth her heart rate was found to be sixty per minute; irregularity of the cardiac sounds was noticed and a questionable murmur was heard over the precordium. Otherwise she was a normal newborn baby.

Three previous pregnancies ended with the delivery of normal full term infants. Unfortunately, this fourth pregnancy did not have medical supervision, so that a record of the fetal heart rate during pregnancy is not available.

The patient was first seen at Children's Hospital on April 26, 1957 at 2½ months of age because of respiratory distress of one day duration.

On admission physical examination, she was a slightly undernourished infant who was not acutely ill. Her nose was stuffy and her throat was mildly erythematous. Respirations were shallow; respiratory rate was 40 per minute. A few dry rales were heard in the base of the right lung. The heart rate was regular at 56 beats per minute. A questionable systolic murmur was heard along the left sternal border. Occasional atrial contractions were audible at the apex. The heart rate did not change while the infant was crying or after atropine administration. Blood pressure was 90/60. The liver and spleen were not palpable. The remainder of the physical examination was normal.

A chest roentgenogram showed bilateral bronchopneumonia and moderate enlargement of the heart. An electrocardiogram showed complete heart block with a ventricular rate of 50 per minute and an auricular rate of 200 per minute. High peaked P waves in Lead II and V_2 were suggestive of right auricular hypertrophy. The QRS complex was supraventricular in form.

After 16 days of hospitalization the infant's pneumonia had responded satisfactorily to tetracycline therapy and she was discharged to be followed in the cardiac clinic. No cyanosis or cardiac failure had been observed during her entire hospital stay. Discharge diagnoses were congenital complete heart block with possible septal defect, and bilateral bronchopneumonia.

COMMENT

Complete heart block should be considered when there is a prenatal slowing of the fetal heart rate *without* diminution of intensity. This is of particular importance since misdiagnosis of fetal distress could lead the obstetrician to perform an unnecessary caesarean section.

* Formerly, Resident.

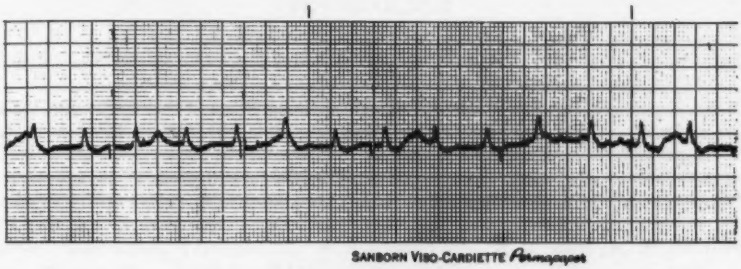


FIG. 1. Electrocardiogram showing complete heart block

A diagnosis of congenital complete heart block is made on the basis of the following criteria: a) A heart rate less than 80 beats per minute in infants or less than 60 beats per minute in older children, b) Electrocardiographic evidence of complete atrioventricular dissociation, c) The presence of an associated congenital heart defect, d) Absence of a history of an infection such as diphtheria, rheumatic fever, or syphilis; e) The occurrence of syncopal attacks with bradycardia in a young child.

Statistics indicate that 8 to 36 per cent of reported cases of complete heart block are congenital. In the majority of cases, there is an associated congenital heart lesion; an intraventricular septal defect is present in over 50 per cent of the patients.

Postmortem histologic examination of the heart has been performed in several cases; the most common cardiac abnormality has been a fibrous body separating the A-V node from the bundle of His. Some hearts have had complete absence of the bundle of His. Aneurysm of the sinus of Valsalva has also been noted.

The ventricular rate may or may not be altered by fever, crying, exercise or drugs. The systolic blood pressure may be elevated and the peripheral pulses may be of the water-hammer type. Jugular venous pulsation is a rather common finding. The QRS complex of the electrocardiogram is supraventricular in form in 99 per cent of the patients.

Stokes-Adams attacks are present in 20 per cent of the cases; when such attacks occur the prognosis is unfavorable due to the possibility of sudden death. In the absence of syncopal attacks these patients are usually asymptomatic. The prognosis depends on the associated lesion. Cardiac failure is a very rare complication. Several patients followed up to the age of 40 years have led normal lives.

No specific therapy is available at the present time. Ephedrine and epinephrine are the drugs of choice in prevention and treatment of the Stokes-Adams attacks.

BIBLIOGRAPHY

BERNEITER, M.: Congenital Heart Block. J. A. M. A., **150:** 792, 1952.

DONOSO, E., BRANNWALD, E., JICK, S., AND GRISHMAN, A.: Congenital Heart Block. Am. J. Med., **20:** 869, 1956.

HAYS, L.: Report of Three Cases of Congenital Heart Block. J. Pediat., **4:** 380, 1934.

LYON, R. A., AND KAPLAN, S.: Nelson Textbook of Pediatrics. Sixth Edition. W. B. Saunders, Philadelphia, p. 914, 1954.

MOSS, A. J., AND LITMAN, N. N.: Congenital Heart Block. J. Pediat., **48:** 226, 1956.

NICHAMIN, S. J.: Stokes-Adams Syndrome Associated with Congenital Complete Heart Block in Infancy and Childhood. Pediatrics, **1:** 327, 1948.

STADLER, H. E., REID, C. A., AND FRIEDMAN, H. P.: Prenatal Fibroelastosis ("Fetal Endocarditis") Manifested Clinically by Total Heart Block. J. Pediat., **36:** 370, 1950.

CHILDREN'S HOSPITAL WASHINGTON 9, D. C.

Announcement

1957 Clinical Proceedings **Attractively Bound Volumes**

Orders are now being taken for bound volumes of the 1957 issues of Clinical Proceedings (277 pages).

The volumes will have a durable and attractive hard cover suitable for display in office or inclusion in a den library. Perhaps you would like to order the 1957 volume for yourself or for a young friend or colleague. The cost will be five dollars.

Will you please send your order and check; payable to Clinical Proceedings, Children's Hospital, before March 15, 1958.

Please Clip and Return this form to the CLINICAL PROCEEDINGS, CHILDREN'S HOSPITAL

Please send one bound volume of the 1957 Clinical Proceedings to:

NAME_____

ADDRESS_____

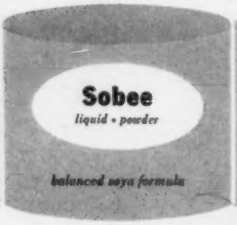
GIFT OF_____

THE MEAD JOHNSON FORMULA PRODUCTS FAMILY FOR EVERY INFANT FEEDING NEED

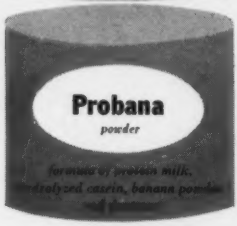
for routine infant feeding ▼

Infant feeding experience for the past 50 years provides the background for the Mead Johnson Formula Products Family. Today, you can meet your feeding needs for both well and sick babies with convenient Mead Johnson formulas. Each product provides an authoritative formulation, and is manufactured with meticulous care to meet the highest standards of nutritional and pharmaceutical excellence.

for allergic infants ▼



for chronic digestive disorders ▶



MEAD JOHNSON
SYMBOL OF SERVICE IN MEDICINE

MEAD JOHNSON & COMPANY, Suite 422 Eig Building, 8641 Colesville Road
Silver Spring, Maryland. JUniper 9-1222